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*Case Report*

# Phenytoin Induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome: A Case Report

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## ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic and rare drug reaction that can be severe and life-threatening if untreated. We present a 34 year old male patient, who developed DRESS syndrome after receiving phenytoin for 8 weeks and presented with rapidly progressive erythematous rash on trunk, face and upper extremities, fever and facial swelling. Abnormal laboratory findings, RegiSCAR score, and Naranjo's probability scale revealed the association between phenytoin and DRESS syndrome. Phenytoin was withdrawn and adequately managed with systemic corticosteroids, antihistamine, and other symptomatic treatments. DRESS syndrome can be cured completely by early detection and removal of culprit drug along with other adequate symptomatic treatments.

**Key words:** DRESS syndrome, Naranjo probability, Hypersensitivity reaction, Scale, Phenytoin, RegiSCAR score.

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## INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic, rare and life-threatening hypersensitivity reaction.[1] It is presented by systemic symptoms that include fever, urticarial maculopapular rash, erythroderma, swelling, facial edema, lymphadenopathy, hepatitis, and abnormal hematological findings such as atypical lymphocytosis and eosinophilia.[2] Anticonvulsants, sulphonamides, antiretrovirals, and non-steroidal anti-inflammatory drugs are known to cause DRESS syndrome.[3] Phenytoin is one of the most commonly prescribed anticonvulsant agents to treat seizure disorders. The incidence of phenytoin-related DRESS syndrome is 1/5000 and the mortality rate of 10%.[4] The specific mechanism of DRESS syndrome is still unclear. However, it appears to be heterogeneous due to immunological complexity.[5] The clinical features of DRESS vary depending upon the involvement of multiple organs that may be present for a long latent period. The heterogeneous nature of reaction makes it difficult to diagnose and treat, which can be sometimes fatal.[6] Hence, we aim to report a case of phenytoin induced DRESS syndrome to understand the clinical manifestations and their management.

## CASE REPORT

A 34 year old male patient came with the complaints of a rapid progressive erythematous rash on trunk, face and upper extremities, fever (38.9°C) on and off with chills from past two weeks and facial swelling from past three days. Patient medical history revealed that he was diagnosed with epilepsy two months back and received a loading dose of Phenytoin 1000 mg IV and maintenance dose of 300 mg/day orally. He was not known for any allergies. During the physical examination, vital signs were found to be normal [pulse rate: 97 bpm and blood pressure: 110/70 mmHg]. Further, on dermatological examination, the patient was found with multiple erythematous maculopapular rashes over the face [Figure 1 (a)], trunk [Figure 1 (b)], back (Figure 1 (c)] and upper limbs (Figure 1 (d)]. He was also found with facial, lips, and periorbital swelling. Abnormal laboratory findings are presented in Table 1. The RegiScar score shows probable (Score: 5) relation between phenytoin and DRESS syndrome. Further, Naranjo's probability scale assessment provided a score of 'seven' suggesting a probable association between phenytoin and DRESS syndrome.

Phenytoin was stopped and he was treated with the Injection Betamethasone 1cc (4 mg/ml) once daily for eight days, prednisolone 10 mg twice daily for seven days followed by 20 mg twice daily for three days and cetirizine 10 mg once daily along with other symptomatic treatments. After nine days of the treatment, patient was symptomatically better [Figure 2 (a)], trunk [Figure 2 (b)], back [Figure 2 (c)] and upper limbs [Figure 2 (d)]. Patient was discharged after 10 days of the hospital stay with tablet clobazam 10 mg once daily along with prednisolone 20 mg twice daily, cetirizine 10 mg once daily, and other symptomatic treatments.

## DISCUSSION

Cutaneous drug reactions pertaining to drugs comprise 2-3% of all reported adverse drug reactions.[7] DRESS syndrome is a severe cutaneous drug reaction that may be associated with multiple organ involvement which may cause chronic illness, trama and infections.[8] It is categorized as a delayed-type IV b hypersensitivity reaction mediated by T helper cells.[9] The estimated incidence of overall DRESS syndrome is 1/1000 to 1/10,000 of drug exposure.[10] Patient presenting with DRESS syndrome may experience fever in the earlier stage of reaction followed by severe rashes along with other systemic symptoms within 2-8 weeks of culprit drug ingestion. The mechanism of DRESS syndrome is still unclear but the possible mechanism can be due to deficiency of detoxifying enzymes,

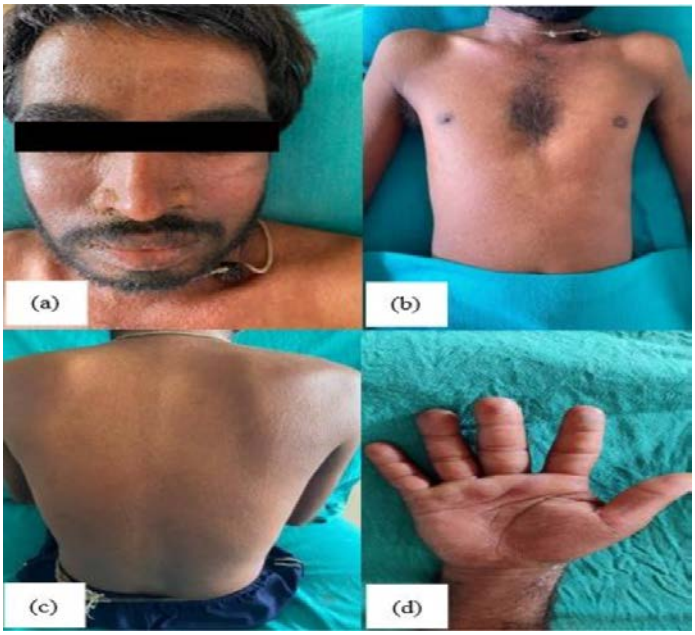


**Figure 1:** Before Treatment, multiple erythematous papule rashes over (a) face, (b) trunk, (c) over back and (d) upper Limb.

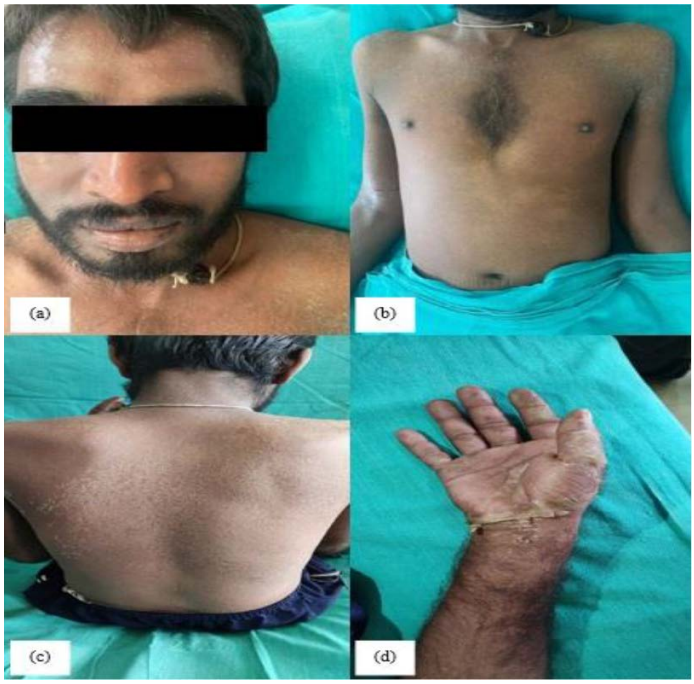


**Figure 2:** After treatment, multiple erythematous papule rashes over (a) face, (b) trunk, (c) over back and (d) upper Limb.

**Table 1: Abnormal laboratory findings.**

| Parameters | At admission | Day-3 | Day-6 | Day-9 | Reference values |
|---|---|---|---|---|---|
| **Hematologic test** | | | | | |
| TLC | 10600 | 24960 | 10760 | - | 4000-11000 cells/mm$^3$ |
| Eosinophils | 0.820 | 1.000 | 1.000 | - | 0.020-0.500 x 10$^3$/µL |
| **Liver Function Tests** | | | | | |
| Total Bilirubin | 4.37 | 6.21 | 6.13 | 3.05 | 0 to 1.2 mg/dl |
| Direct Bilirubin | 4.17 | 6.35 | 6.28 | 2.96 | 0 to 0.2 mg/dl |
| AST | 300 | 197 | 168 | 107 | 0 to 32 U/L |
| ALT | 456 | 311 | 311 | 258 | 0 to 33 U/L |
| ALP | 376 | 374 | 386 | 294 | 35 to 104 U/L |

accumulation of drug metabolites, genetic association between human leukocytes and drug hypersensitivity or it can be due to a virus-drug interaction leading to viral reactivation.[8] In this report, patient presented with rapidly progressive rashes, fever and facial swelling after taking phenytoin (approximately, cumulative dose of 16,800 mg) for 8 weeks. The association between phenytoin and DRESS syndrome was evaluated by using RegiSCAR scoring system, which is used as the diagnostic criteria for DRESS syndrome. In this patient, obtained RegiSCAR score was 'five' suggested probable association between DRESS syndrome and exposed drug (phenytoin). It includes eosinophilia 0.820 cells x 103/µL (score 1), atypical lymphocytosis (score 1), skin rash extended > 50% Body Surface Area (score 1), skin rash suggesting DRESS (score 1), organ involvement (score 1), rash resolution ≥ 15 days (score -1) and excluding other causes like HIV, Hepatitis B, Hepatitis C and Epstein-Barr virus infection (score: 1). The affected internal organ was the liver which was determined by liver function tests showing transaminitis and hyperbilirubinemia. The causality assessment by Naranjo's algorithm showed a probable (score: 7) association between phenytoin and DRESS syndrome. Severity of DRESS syndrome was found to be moderate (level 4 b) according to the Modified Hartwig and Siegel scale. Phenytoin induced DRESS syndrome has been reported,[5] but due to lack of awareness and inadequate monitoring of phenytoin serum concentration, increases the risk of rare reaction like DRESS syndrome. Earlier detection of DRESS syndrome can reduce the severity and prevent the organ failure. The mainstay of the treatment for DRESS syndrome includes withdrawal of the offending drug, administration of steroid and symptomatic treatment.[1,5] Withdrawal of the drug and subsequent improvement of clinical characteristics of DRESS reaction makes the diagnosis more significant. In this case, phenytoin was withdrawn and treated with the steroid for 10 days, an antihistamine for 10 days, another class of anti-seizure drug and symptomatic treatment. Further, clinical pharmacists critical role in the detection and management of such adverse reactions to ensure drug safety.[11,12] Therefore, in this study clinical pharmacist provided the counseling about adverse drug reaction to this patient and his caretaker. He was also provided with the alert card and was advised to produce it to the physician or the pharmacist to prevent re-exposure of phenytoin.

## CONCLUSION

Phenytoin was a causative agent of the DRESS syndrome in this patient and the progression of conditions can be severe and life-threatening. It requires early detection and aggressive treatment that includes the withdrawal of suspected drug, use of steroids, and adequate supportive treatment. Further, patient should be prevented from re-exposure to culprit drugs to avoid such reactions.

### Declaration of patient consent

The authors certify that they have obtained appropriate consent from the patient for clinical information and his images to be reported in the journal.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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